REMARKS

Claims 1, 2, 5-7, and 10-26 are pending in the application. Claims 1, 2, 5-7, and 10-26 stand rejected.

I. Response to rejection under 35 U.S.C. § 103(a)

A. Rejection over US 5,861,179

The Examiner alleges that claims 1, 2, 5-7 and 10-15 are obvious over US patent 5,861,179 (Hiskett *et al.*) Applicants respectfully traverse.

Certain criteria should be considered to establish *prima facie* obviousness. First, there should be some reason that would have prompted a person of ordinary skill in the art, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the elements as the new invention does. Second, there must be a reasonable expectation of success. Third, the prior art reference(s) must teach or suggest all claim limitations (MPEP 706.02(j)).

Hiskett *et al.* teach a formulation of lamotrigine that is prepared by spray granulation of a mixture of lamotrigine, lactose, starch, and crystalline cellulose in the presence of the binder polyvinylpyrrolidinone. Hiskett *et al.* disclose (col. 3, line 25-30) that these components used in preparing the formulation are themselves provided "as powders having particle sizes..."

Hiskett *et al.* disclose a broad range for the particle size for lactose (col. 3, line 60) as "below 250μm, especially 200μm or less, such as 50 to 200μm." Hiskett *et al.* also disclose (Table at top of column 4) additional particle size ranges for two specific lactose species (DCL 21 and DMV200). Hiskett *et al.* disclose broad particle size ranges for starch (30-150μm; col. 4, line 12) and for crystalline cellulose (40-100μm; 50-90μm and 90μm; at col. 4, line 18-19).

Hiskett *et al.* do not disclose or suggest any range of particle sizes for lamotrigine, but rather only disclose one particle size, specifically, lamotrigine 125μm (defined by Hiskett as "lamotrigine having particle sizes up to 125μm").

Independent claims 1 and 6 recite lamotrigine particles having a diameter equal to or less than 50μm. The recited 50μm maximum particle size would be 60% smaller than the 125μm particle size disclosed by Hiskett *et al.* Accordingly, Hiskett fails to teach or suggest all of the claim limitations because there is no teaching or suggestion of the recited 50μm maximum particle size.

The Examiner alleges that the skilled person would have been motivated to "optimize the particle size of the lamotrigine particles because the optimization step is considered well in

the competence level of an ordinary skilled artisan in the pharmaceutical science," and it is "within the skill in the art to select optimal parameters, such as the amount of ingredients, granular size and specific surface area, in a composition in order to achieve a beneficial effect of increased dissolution."

However, Hiskett *et al.* provide no motivation to modify the lamotrigine particle size. In stark contrast, Hiskett *et al.* provide motivation to vary nearly every other component of the disclosed compositions. For example, Hiskett *et al.* provide broad ranges for particle sizes of all of the other powdered components (starch, crystalline cellulose and lactose) in the disclosed powder formulations. But Hiskett *et al.* provided only a single particle size for the lamotrigine, *i.e.*, "lamotrigine 125 μm."

Hiskett *et al.* also provide varied parameters for amounts of components in the disclosed formulations. For example, a broad range is provided for the amount of lamotrigine, *i.e.*, 0.5 to 50% by weight (column 2, line 1) as well as broad ranges for the proportions of the other components of the Hiskett formulation. But, though a broad range is provided for the amount of lamotrigine in the formulation, still only one lamotrigine particle size is disclosed.

Hiskett *et al.* prepared five different powders as working examples, and varied several parameters in these different powders. The varied parameters included, for example, the amount and composition of lactose, the amount and type of starch, and the type of crystalline cellulose. But in all of the working examples, the lamotrigine that was used had the same particle size, *i.e.*, "lamotrigine 125μm."

Hiskett *et al.* analyzed the disclosed formulations to assess the effect of temperature, humidity and artificial light on the stability of each. Four parameters were assessed: appearance, hygroscopicity, purity (HPLC) and dissolution. Hiskett *et al.* specifically addressed how these parameters varied for the different formulations that were prepared and tested. For example, at column 6, line 46, Hiskett *et al.* described appearance changes that occurred in all the formulations, and noted that formulation B more easily changed color. At column 6, line 46, Hiskett *et al.* stated that formulation E was the most hygroscopic, and at line 59-61 added that formulation E was the most stable and formulation A was the least stable. At column 6, line 66, Hiskett *et al.* stated that "[a]ll the formulations showed rapid dissolution."

Thus, Hiskett *et al.* teach varying numerous parameters in the optimization of the disclosed formulations. Hiskett *et al.* further teach assessing of the effect of varying those parameters on the appearance, purity, hygroscopicity and solubility of the formulation. But,

Hiskett *et al.* do not teach or suggest any variation in the lamotrigine particle size, and thus do not teach any optimization that might be correlated with lamotrigine particle size.

The Examiner alleged that it was within the skill in the art to optimize lamotrigine particle size to "achieve a beneficial effect of increased dissolution." However, none of the parameters varied by Hiskett *et al.* were reported to have any effect on dissolution. Also, the particle size of lamotrigine was not among the numerous parameters that were optimized by Hiskett *et al.*, even though Hiskett *et al.* were expressly assessing the disclosed lamotrigine formulations for solubility as well as appearance, purity and hygroscopicity.

Applicants do not believe that Hiskett *et al.* would have provided any suggestion or motivation to the skilled person to reduce the lamotrigine particle size, or even to modify the particle size, either to make the particle size larger or smaller. Furthermore, Applicants do not believe that Hiskett *et al.* would have provided any suggestion or motivation to reduce the lamotrigine particle size by 60% as would be required to make the claimed invention.

Moreover, the Hiskett *et al.* assessment of variation in stability of the disclosed formulations, as a function of the variations in various components of the formulations, fails to provide any reasonable expectation of success if one were to vary a different parameter, such as lamotrigine particle size.

If anything, Hiskett *et al.* may teach away from modifying lamotrigine particle size, by providing broad ranges for so many other parameters, but always maintaining the same lamotrigine particle size in all the prepared formulations, and not disclosing or suggesting any other suitable particle size for the lamotrigine.

Accordingly, the Examiner has not provided a *prima facie* case for obviousness over Hiskett *et al.*, and Applicants therefore respectfully request that the rejection of claims 1, 2, 5-7 and 10-15, under 35 USC 103(a) be reconsidered and withdrawn.

B. Rejection over US 5,861,179 in view of US 4,602,017

The Examiner alleges that claims 16-24 are obvious over (Hiskett *et al.*) in view of US 4,602,017 (Sawyer *et al.*). Applicants respectfully traverse.

The Examiner stated that Sawyer *et al.* teaches the use of compounds according to a generic structure that embraces lamotrigine, for treatment of CNS disorders, and further teaches solid and liquid pharmaceutical formulations.

Nothing in the Sawyer *et al.* reference provides what is missing from Hiskett *et al.* regarding the compositions of independent claims 1 or 6, nor contradicts the teaching-away by

Hiskett *et al.*, based on the Hiskett *et al.* teaching of varying many parameters in solid lamotrigine formulations, but always maintaining the same lamotrigine particle size. Accordingly, neither independent claims 1 and 6, nor any claim, *e.g.*, claims 16-24, that depends from those independent claims, can reasonably be deemed obvious in view of these two references.

Applicants therefore respectfully request that the Examiner withdraw the obviousness rejection of claims 16-24 over Hiskett *et al.* in view of Sawyer *et al.*

Applicants respectfully submit that, in light of the above remarks, the present Application is in condition for allowance.

This Amendment is being timely filed in view of the accompanying Petition under 37 CFR 1.136 for a three-month extension of time, which extends the time for a response to the Office Action through and to October 11, 2007.

Please charge the fee for the three-month extension, and any other fees, including the RCE filing fee, which may be required for the filing of this response, to Kenyon & Kenyon, LLP Deposit Account No. 11-0600.

Respectfully Submitted,

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